REMARKS/ARGUMENTS

Claims 1-2, 4, and 6-25 are pending.

Claim 1 has been amended.

Claims 3 and 5 have been cancelled.

Support for the amendments is found in the claims and specification (e.g., pages 1-2, paragraphs [0003]-[0005] and the Examples), as originally filed.

No new matter is believed to have been added.

Applicants wish to thank the Examiner for the discussion on May 3, 2011. The Applicants' representative explained the invention. The prior art rejections were discussed in view of the proposed amendments. It was explained that the limitation "that solubilize" of claim 1 is not an "active method step". It was suggested amending claim 1 by reciting "the components that solubilize."

Claims 1-2, 4, and 6-25 are rejected under 35 U.S.C. 101 as directed to non-statutory subject matter. Applicants respectfully traverse.

The limitation "as the components that solubilize" of claim 1 is not "an active method step" but it merely further explains that irinotecan is in a soluble form in the injectable aqueous preparation which has a pH of 2-5 and irinotecan is solubilized due to the presence of acetic acid and sodium acetate.

Applicants request that the rejection be withdrawn.

Claims 1-2, 4, and 6-25 are rejected under 35 U.S.C. 103(a) over Chen et al., US 6,383,471, and Li et al., Am. J. Health Syst. Pharma., 59:539-544 (2002). The rejection is traversed because the combination of the references does not describe or suggest

(i) an injectable aqueous solution preparation comprising acetic acid and sodium acetate as the components that solubilize 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin in the aqueous solution of the acetic acid and sodium acetate at a pH of 2 to 5; and

(ii) the concentration of 1-50 mg/ml of 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin in the preparation (as in claim 24).

(iii) The claimed preparation provides an unexpected result.

(1) Chen et al. describe an oral preparation of ionizable hydrophobic agents (see col. 4). The Chen et al. formulations comprise the ionizable hydrophobic agents and a carrier which includes a surfactant that is capable of solubilizing the hydrophobic agents, and an ionizing agent. Col. 4, ln. 29-41.

The Office has alleged that an ionizing agent for deprotonating the acidic functional groups can be acetic and ascorbic acid (col. 11, ln. 21-22) and that sodium acetate is a carrier (Table 20). Based on these disclosures, the Office concluded that Chen et al. describe all of the limitations of claim 1 except an injectable solution having a pH of 2-5. Applicants respectfully disagree.

Chen et al. describe that irinotecan is an example of an agent having at least one ionizable basic group (col. 7, ln. 50 to col. 10, ln. 19). Ionizing agents that protonate the basic functional groups of a therapeutic agent are inorganic and organic acids (e.g., acetic and ascorbic acids), while ionizing agents that deprotonate the acidic functional groups are organic and inorganic bases which can be salts of organic and inorganic acids (e.g., salts of acetic and ascorbic acids). Col. 11, ln. 9-44.

Thus, Chen et al. describe that the ionizing agents for the therapeutic agents having basic functional groups, including irinotecan, can be acetic and ascorbic acids. Chen et al. do

not describe that the ionizing agents for the therapeutic agents including irinotecan can also include a salt of these acids.

The Office has pointed to Table 20 as describing sodium acetate as a carrier. Table 20 describes 70 possible carrier compositions, wherein a specific carrier is selected depending upon the properties of a therapeutic agent. For example, for itraconazole also having basic functional groups (as irinotecan), carriers 27-31 were selected which do not comprise acetic acid and/or sodium acetate. For tretinoin having acidic functional groups, carriers 65-66 were selected which also do not comprise acetic acid or sodium acetate. Thus, carriers 37, 43, and 60 which include sodium acetate are not used for solubilizing irinotecan. In addition, carriers 37, 43, and 60 do not include acetic acid.

(2) Further, Chen et al. describe a large number of possible therapeutic agents, ionizing agents, solubilizers, and surfactants. However, Chen et al. do not describe or suggest selecting the specific claimed composition of irinotecan and acetic acid and sodium acetate with a reasonable expectation of solubilizing irinotecan to provide an injectable aqueous solution.

Modifying the Chen et al. composition would not have been obvious. Specifically, it is not "obvious to try" a particular combination when a person of ordinary skill in the art is presented with a large number of unidentified, unpredictable solutions, without guidance and a reasonable expectation of success and/or "where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

Even post KSR, for a claimed invention to be obvious, the possible modifications of the prior art must be finite. *See, Rolls-Royce PLC* v. *United Technologies Corp.*, 95 USPQ2d 1097 (Fed. Cir. 2010). As stated by the Federal Circuit:

> *To determine that an invention would have been obvious* to try on the basis of the record before the time of invention, *this court has clarified,* with respect to inventions requiring selection of a species from a disclosed genus, *that the possible approaches and selection to solve the problem must be* "known *andfinite." See Abbott,* 544 F.3d at 1351 (holding as conditions in which "obvious to try" may negate patentability, "the problem is known, the possible approaches to solving the problem are known and finite, and the solution is predictable through use of a known option"). ... In this case, the broad selection of choices for further investigation available to a person of ordinary skill included any degree of sweep. *See Takeda,* 492 F.3d at 1359 (holding the invention not obvious to try because the prior art disclosed a broad selection of compounds that an ordinarily skilled artisan could have selected for further investigation).

Rolls-Royce, at 1107, (emphasis added).

This case is like that in *Rolls-Royce* in that there are countless possible theoretical combinations of the prior art with no teaching that anyone combination should be selected.

Thus, Chen et al. do not describe a carrier for a therapeutic agent having basic functional groups comprising acetic acid and sodium acetate, not to mention, without using surfactants and additional solubilizers to solubilize irinotican.

In addition, based on the disclosure for one therapeutic agent, a skilled artisan would not have reasonably expected that the same composition would have provided solubilization of a different therapeutic agent because the chemical arts are unpredictable. The Court stated that "[t]o the extend an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co, Ltd. v. Dr. Reddy's Lab.*, 533 F.3d. 1353 (Fed. Cir. July 21, 2008).

(3) Concerning the disclosure of Li et al., Li et al. studied stability of irinotecan *hydrochloride*, which is an injectable solution having a concentration of 20 μg/ml, i.e., already solubilized before the pH is adjusted to below 6, diluted with phosphate buffer

solutions to a pH 4, 6, and 7.4 and that the lower pH should prevent hydrolysis of irinotecan. Abstract, pages 541 and 543, and Table 1.

Although Li et al. suggest using a pH below 6, Li et al. also suggest using a phosphate buffer for adjusting this pH of already solubilized irinotecan hydrochloride. Thus, Li et al. suggest using a phosphate buffer to stabilize already solubilized irinotecan (possibly by heating or in an alkaline solution).

Irinotecan is not easily soluble in aqueous solutions and heating is required to prepare an aqueous solution (see page 2 of the present specification). For example, Ahmad et al., previous cited by the Office, describe that a typical aqueous solution for dissolving irinotecan is alkaline. Thus, it is reasonable to conclude that a solution of irinotecan hydrochloride in Li et al. should be alkaline or at least prepared by using heat.

(4) Also, the present specification shows that when an acid different from the claimed acid is used (e.g., lactic, malic, citric, or ascorbic acids) in the Comparative Examples, CPT-11 solution have inferior properties compared to the inventive solutions. Li et al. uses a phosphate buffer which is different from the claimed acid.

Thus, the claimed preparation provides an unexpected result, which is not expected based on the disclosure of the cited references.

(5) Concerning **claim 24**, Li et al. describe that a low concentration solution of 20 μg/ml of irinotecan is used. However, in the present invention, the stability of a solution having a high concentration of 1-50 mg/ml of irinotecan without heating has been studied. See [0023] of the present specification.

Thus, substituting the disclosure of Li et al. in the oral formulation of Chen et al. still does not produce the claimed injectable composition.

Thus, Chen et al. and/or Li et al. do not make the claimed preparation obvious.

Applicants request that the rejection be withdrawn.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

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